DACOGEN® (decitabine)

United States Food and Drug Administration
Oncologic Drugs Advisory Committee

February 9, 2012

NDA #21790/S-010

Eisai

Introduction

Alton Kremer, MD, PhD

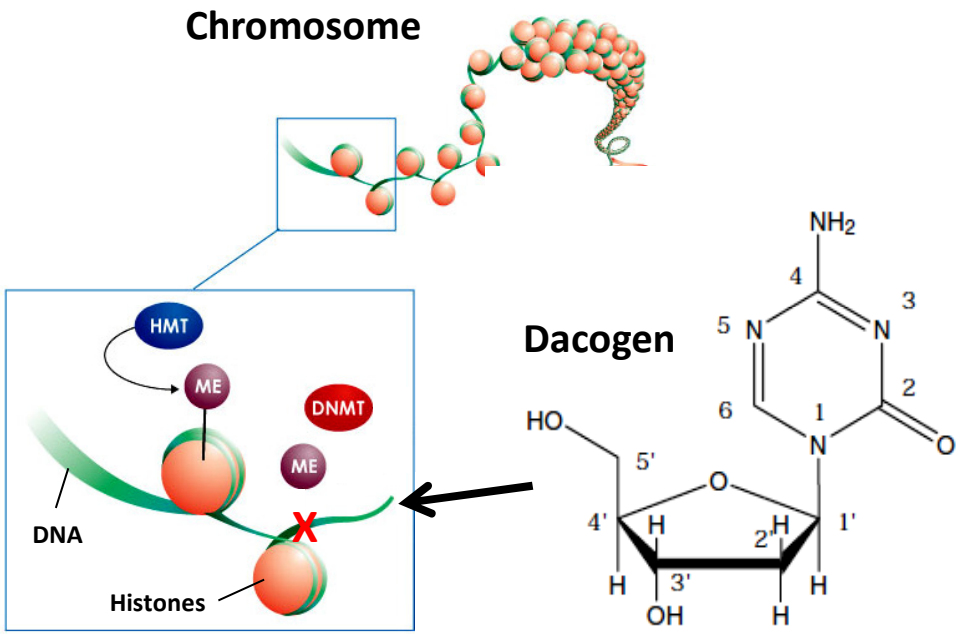
Senior Vice President, Clinical Development, Oncology
Eisai Inc.

Agenda

Introduction	**Alton Kremer, MD, PhD** Senior Vice President Clinical Development, Oncology Eisai Inc.
AML Disease Background	**William Blum, MD** Associate Professor of Medicine Division of Hematology The Ohio State University
Dacogen (decitabine) Efficacy and Safety	**Peter Tarassoff, MD, PhD** Executive Director Clinical Development, Oncology Eisai Inc.
Benefit/Risk	**Alton Kremer, MD, PhD**
Statistical Consultant	**L J Wei, PhD** Professor of Biostatistics Harvard University

Dacogen (Decitabine) is a Hypomethylating Agent

- Incorporated into DNA during replication and RNA during transcription
- Inhibits activity of methyltransferase causing hypomethylation, and cellular differentiation or apoptosis
- Reverses silencing of genes critical for the control of cellular differentiation and proliferation



HMT = histone methyltransferase; DNMT = DNA methyltransferase.
Data on file. Eisai Inc., Woodcliff Lake, NJ; 2009.

Dacogen Proposed and Current Indications

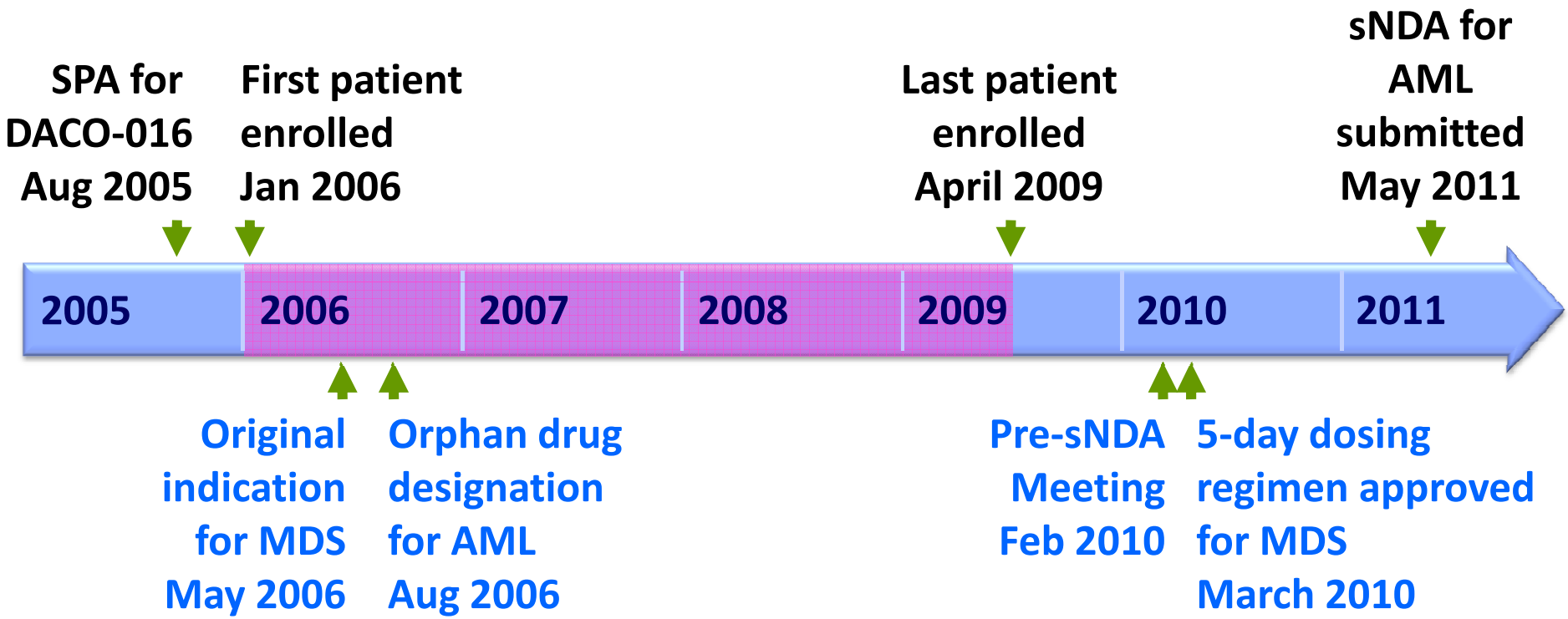
Proposed indication

- Dacogen is indicated for treatment of acute myelogenous leukemia (AML) in adults ≥ 65 years of age who are not considered candidates for induction chemotherapy

Current indication

- Dacogen is indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

Dacogen Regulatory History



Overview of Dacogen Clinical Development Program in AML

Study	N	Phase	Description
016	485	3	• Randomized, open-label, multicenter, multinational study in patients ≥ 65 years of age with newly diagnosed de novo or secondary AML and intermediate- or unfavorable-risk cytogenetics • Comparator: treatment of choice (TC) • Primary endpoint: overall survival (ITT)
017[1] (supportive)	55	2	• Single-arm, open-label, multicenter study in patients ≥ 60 years of age with newly diagnosed de novo or secondary AML and intermediate- or unfavorable-risk cytogenetics • Primary endpoint: morphologic CR (ITT)

CR = complete remission; ITT = intention to treat.

1. Cashen AF, et al. *J Clin Oncol*. 2010;28:556-561.

Why Are We Here Today?

- Although data show longer survival with Dacogen, the pre-specified primary analysis of Study 016 did not show a statistically significant improvement in OS
- The aggregate clinical data demonstrate benefit over TC, which includes low-dose cytarabine, an accepted standard of care in elderly AML patients
  - Clinically meaningful overall survival (OS) benefit, primary analysis and unplanned updated survival 1 year later
  - Secondary endpoints demonstrating anti-leukemic activity

Why Are We Here Today?

- FDA has identified 2 review issues
  - The statistical interpretation and clinical meaning of the study 016 efficacy result
  - The regional discrepancy in survival results
- Study 016 was a large, randomized, phase 3 trial of Dacogen (an outpatient low-intensity regimen) in elderly patients with AML
  - A large proportion of elderly AML patients do not receive induction chemotherapy, and have limited alternative treatment options
  - In this population Dacogen has demonstrated a favorable benefit-risk profile

AML Disease Background

William Blum, MD

Associate Professor of Medicine
Division of Hematology
The Ohio State University

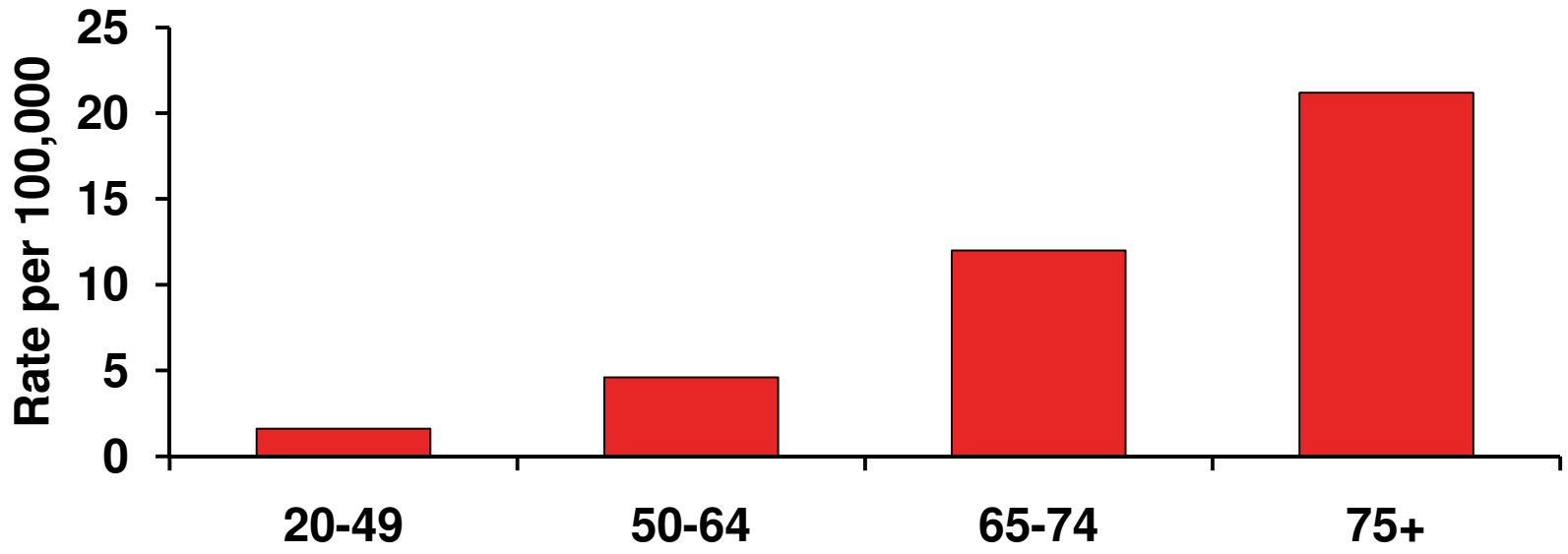
Brief Synopsis

- Incidence and demographics of AML
- Treatment guidelines
- Expected outcomes for older AML patients
  - Do existing data represent the typical patient?
- My own experience with decitabine

Incidence and Demographics of Adult AML

- Approximately 13,000 new cases diagnosed annually in US[1]
- Median age of onset is 65 to 70 years[2,3]

Incidence of AML by age[4]



1. ACS Cancer Statistics 2011.
2. Estey E. *J Clin Oncol*. 2007;25:1908-1915.
3. Craig CM, et al. *Blood Reviews*. 2008;22:221-234.
4. SEER data 2008.

Current NCCN 2011 Guidelines for AML Patients ≥ 60 Years of Age

ECOG PS 0-2 Minimal comorbidity Good-risk cytogenetics *de novo* AML	• Clinical trial • Intensive chemotherapy (7+3) • Low-intensity: low-dose Ara-C, 5-aza, decitabine • Intermediate-intensity: clofarabine
ECOG PS 0-2 Unfavorable cytogenetics Secondary AML	• Clinical trial • Low-intensity: low-dose Ara-C, 5-aza, decitabine • Intermediate-intensity: clofarabine • Intensive chemotherapy (7+3)
ECOG PS > 2	• Clinical trial • Low-intensity: low-dose Ara-C, 5-aza, decitabine • Best supportive care
ECOG PS 0-3 with significant comorbidities	• Best supportive care

NCCN Clinical Practice Guidelines in Oncology™ v. 2.2011. http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.

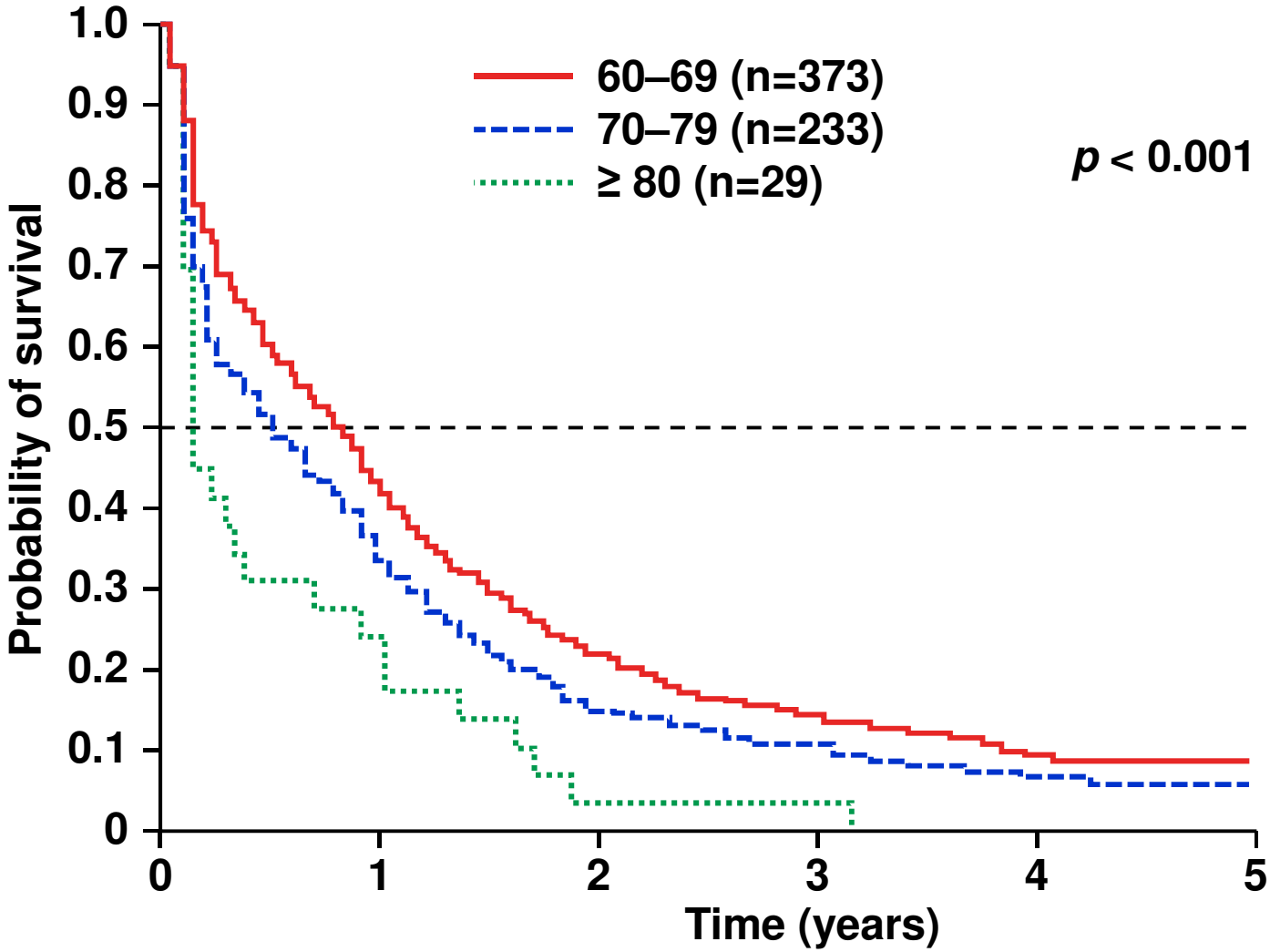
Choice of Therapy for Older AML Patients

- Choice of therapy should account for
  - Performance status
  - Comorbidities
  - Organ function/infections
  - Cytogenetic risk
  - Age

<u>Wishes of the patient and their family</u>

Overall Survival for AML Patients Age ≥ 60 Years Treated with Intensive Induction Chemotherapy

Cancer and Leukemia Group B



Farag SS, et al. *Blood*. 2006;108:63-73.

Limitations of Standard Induction Chemotherapy in Older AML Patients

- Grade 4 myelosuppression is universal and prolonged
- Higher treatment-related mortality rates than younger
- Lower complete remission (CR) rates and survival rates

Outcome	Age 56–65	Age 66–75	Age > 75
Treatment-related death (30-day mortality)	11%	20%	31%
CR rate	46%	39%	33%

Appelbaum FR, et al. *Blood*. 2006;107:3481-3485.

Many Older AML Patients Do Not Receive Chemotherapy

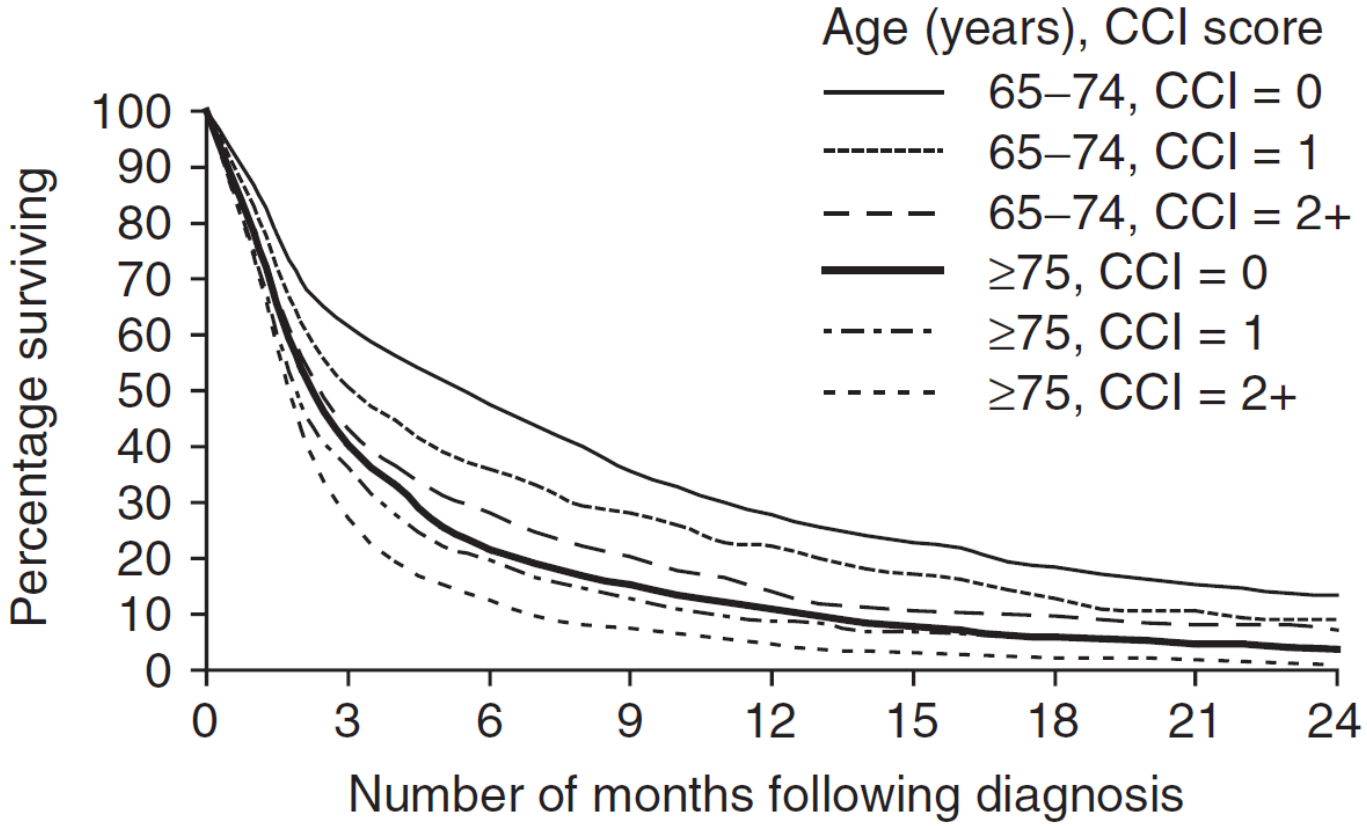
- Retrospective reviews of past Medicare data indicated that only about a third of AML patients ≥ 65 years of age receive chemotherapy within 2 years of diagnosis[1,2]

	Age, years			
	65–74	75–84	≥ 85	Total
Menzin 2002	n=1132 44%	n=1082 24%	n=433 6%	n=2657 30%
Lang 2005	n=1507 49%		n=525 7%	n=3439 34%

1. Menzin J, et al. *Arch Intern Med*. 2002;162:1597-1603.
2. Lang K, et al. *Drugs Aging*. 2005;22:943-955.

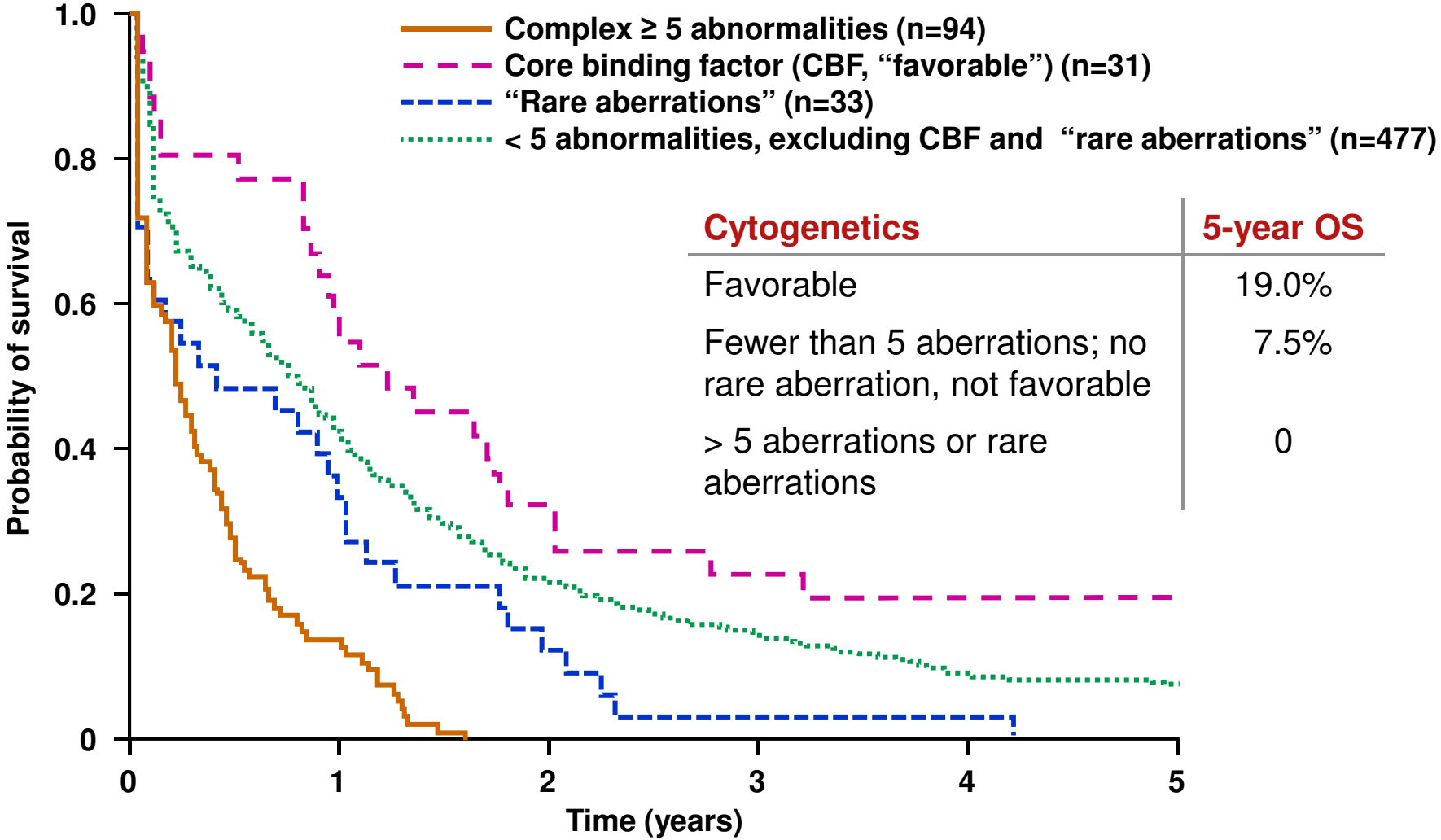
Overall Survival by Age Among Older AML Patients in Medicare Database (N=3439)

Overall median OS = 2.4 months
Overall 2-year survival rate = 7%



CCI = Charlson comorbidity index.
Lang K, et al. *Drugs Aging*. 2005;22:943-955.

Older AML Enriched for Cytogenetic Subsets That Do Poorly With Standard Therapy



Cytogenetics	5-year OS
Favorable	19.0%
Fewer than 5 aberrations; no rare aberration, not favorable	7.5%
> 5 aberrations or rare aberrations	0

Farag SS, et al. *Blood*. 2006;108:63-73.

Low-dose Ara-C Vs Hydroxyurea in Older AML Patients (AML14, Subset)

Study	Median age, years	N	CR, %	Early deaths, %	1-year OS, %
Low-dose Ara-C	74	103	18	26	~25%
Hydroxyurea		99	1	26	~10%

Overall survival: HR = 0.60 (95% CI: 0.44, 0.81); log-rank, 2-sided $p = 0.0009$

Burnett AK, et al. *Cancer.* 2007;109:1114-1124.

Phase 2 Study of Decitabine in Previously Untreated Older AML Patients

- Single institution (Ohio State) trial with 10-day decitabine induction followed by abbreviated cycles in maintenance
- Patients were not candidates/refused standard therapy (N=53)
  - Median age, 74 years (range, 60–85)
  - 36% secondary AML
  - 49% had comorbidity scores ≥ 3 by HCT-CI
- CR = 47% (CR plus incomplete CR = 64%)
  - in all cytogenetic subsets
  - in both *de novo* and secondary AML
- Early death (within 8 weeks) = 15%
- Median survival about 1 year

Blum W, et al. *Proc Natl Acad Sci*. 2010;107:7473-7478.

Conclusions

- The majority of AML patients are older than 60
- Treatment options are limited for these patients
  - Standard induction chemotherapy has high TRM and low CR rates compared with younger patients
  - Long-term survival results are dismal
- Many patients are not candidates or choose not to receive standard induction chemotherapy
- High unmet need for additional effective treatment options with an acceptable safety profile
- Decitabine is a well tolerated hypomethylating agent that has promising activity in AML

DACOGEN® (decitabine) Efficacy and Safety

Peter Tarassoff, MD, PhD

Executive Director, Clinical Development, Oncology
Eisai, Inc.

Overview of Dacogen Clinical Development Program in AML

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016	485	3	• Randomized, open-label, multicenter, multinational study in patients ≥ 65 years of age with newly diagnosed de novo or secondary AML and intermediate- or unfavorable-risk cytogenetics • Comparator: treatment of choice (TC) • Primary endpoint: overall survival (ITT)
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1. Cashen AF, et al. *J Clin Oncol*. 2010;28:556-561.

Study Design
Study 016

Patients (N = 485)
- Age ≥ 65 years
- Newly diagnosed de novo or secondary AML
- ECOG performance status of 0–2
- Intermediate- or unfavorable-risk cytogenetics

Stratification by ECOG PS (0 or 1 vs 2), age (65 – 69 vs ≥ 70 years), and cytogenetic risk (unfavorable vs intermediate).

R
1:1

Dacogen
20 mg/m^2 by 1-hour IV infusion once daily for 5 consecutive days every 4 weeks

Treatment of choice (TC)[a]
- Cytarabine 20 mg/m^2 subcutaneous daily for 10 consecutive days every 4 weeks

OR
- Supportive care (SC)

Treatment until death, relapse, disease progression, unacceptable toxicity, or it was determined that the patient's condition or lack of clinical benefit prevented further treatment.

Two interim analyses were planned and conducted.
a: Patient's choice of treatment selected before randomization.

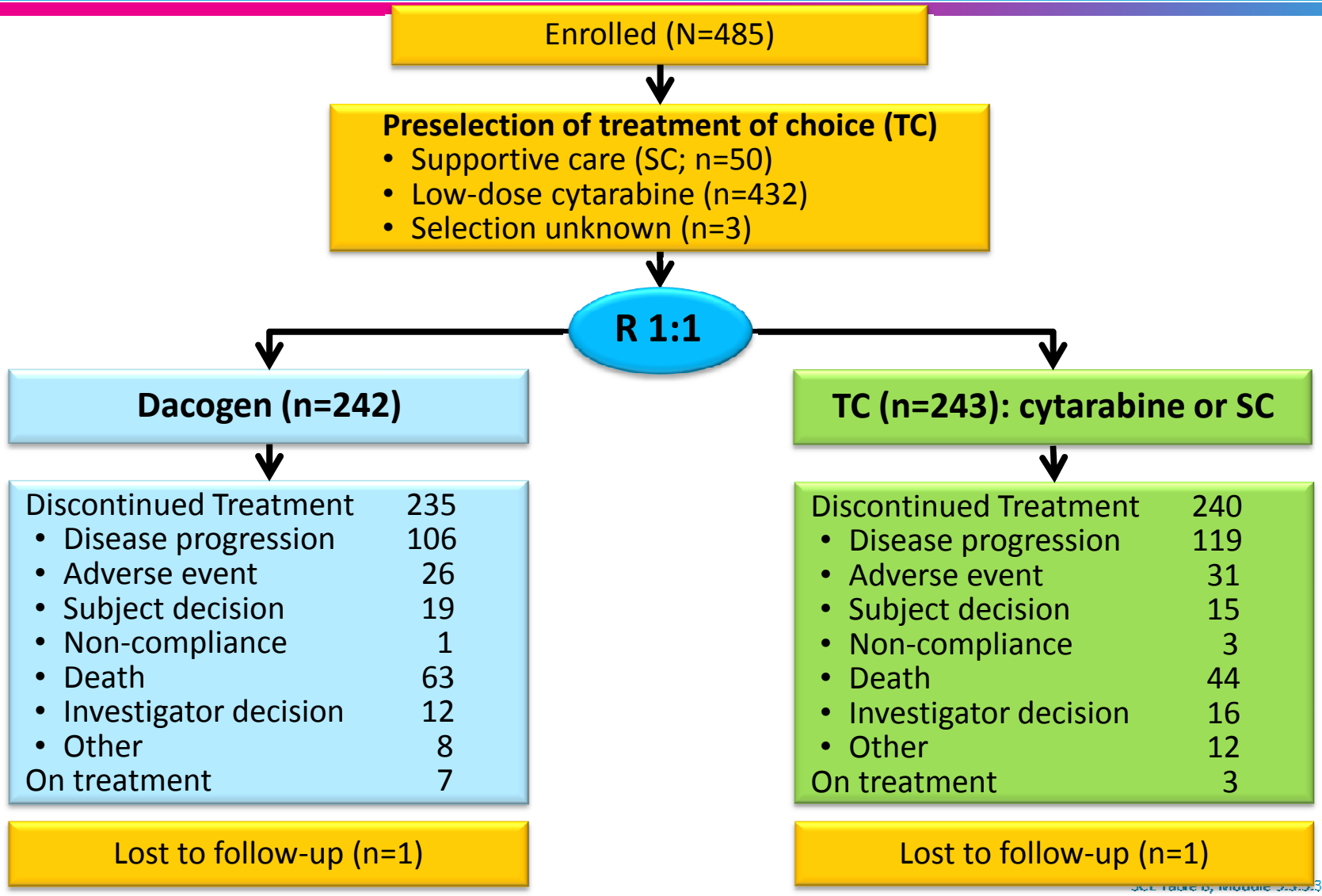
Endpoints
Study 016

- Primary: Overall survival
  - Planned at 385 deaths (actual number 396)
  - Stratified, 2-sided, log-rank test
  - 80% power to detect 25% reduction in mortality risk (assuming median OS of 8 months for Dacogen arm and 6 months for TC arm)
- Secondary:
  - CR + CRp by independent expert review committee
  - Safety
- Tertiary: EFS, PFS, RFS, cytogenetic CR, population PK, quality of life (EORTC QLQ-C30) – at baseline and at cycle 3

CR = complete remission; CRp = complete remission with incomplete platelet count recovery; EFS, event-free survival; PFS, progression-free survival; RFS, relapse-free survival; PK = pharmacokinetics.

Patient Disposition

Study 016 (Clinical Cutoff: 29 Oct 2010)



3.2/Table 1.1.

Baseline Demographics
Study 016

Characteristic	Dacogen (n=242)	Total TC (n=243)
Age, years		
Median (range)	73 (64–89)	73 (64–91)
Age category, % pts		
<65 years	1	< 1
65–69 years	28	28
70–74 years	31	31
75–79 years	27	24
≥80 years	12	17
Sex, % pts		
Male	57	62
Female	43	38
ECOG performance status, % pts		
0	17	19
1	58	54
2	25	27

TC = treatment of choice.

Study 016 CSR, Table 9.

Baseline Disease Characteristics
Study 016

Characteristic	Dacogen (n=242)	Total TC (n=243)
Type of AML, % pts		
de novo	64	65
Secondary	36	35
N/A	0	1
Type of secondary AML, % pts	(n =87)	(n=84)
MDS	68	88
Myeloproliferative disorder	18	10
Prior leukemogenic exposure	14	2
Median WBC count (range), $10^3/\mu L$	3.1 (0.3 – 127.0)	3.7 (0.5 – 80.9)
Blasts in bone marrow – category, % pts	(n =241)	(n=241)
<20	2	3
20–30	27	24
31–50	28	31
>50	44	42
Median blast counts in marrow (range), %	46.6 (3 – 100)	45.0 (0 – 100)
Cytogenetic classification of risk, % pts	(n =241)	(n =242)
Intermediate	63	64
Unfavorable	36	36

Study 016 CSR, Table 10 and 11.

Key Baseline Characteristics by Region

Study 016

Characteristic	E Europe (n=222)	N Am/Australia (n=120)	W Europe (n=85)	Asia (n=58)
Median age, years (range)	71 (64 – 89)	76 (64 – 89)	74 (65 – 85)	73 (64 – 91)
ECOG PS, % pts				
0	7	28	40	9
1	60	54	46	60
2	33	18	14	31
Type of AML, % pts				
De novo AML	74	55	58	57
Secondary AML	26	44	41	43
Cytogenetic risk group, % pts				
Intermediate	64	59	60	74
Unfavorable	36	41	37	26
Mean WBC count, $10^3/\mu L$ (range)	3.9 (0.5 – 126.6)	2.9 (0.3 – 75.5)	2.8 (0.5 – 95.6)	4.0 (0.3 – 25.4)
Mean blasts in marrow (SD)	50.7 (23.28)	51.5 (24.13)	47.6 (24.11)	47.2 (23.25)
Mean Wheatley Score (SD)	9.3 (2.68)	10.0 (2.49)	9.8 (2.47)	9.5 (2.34)

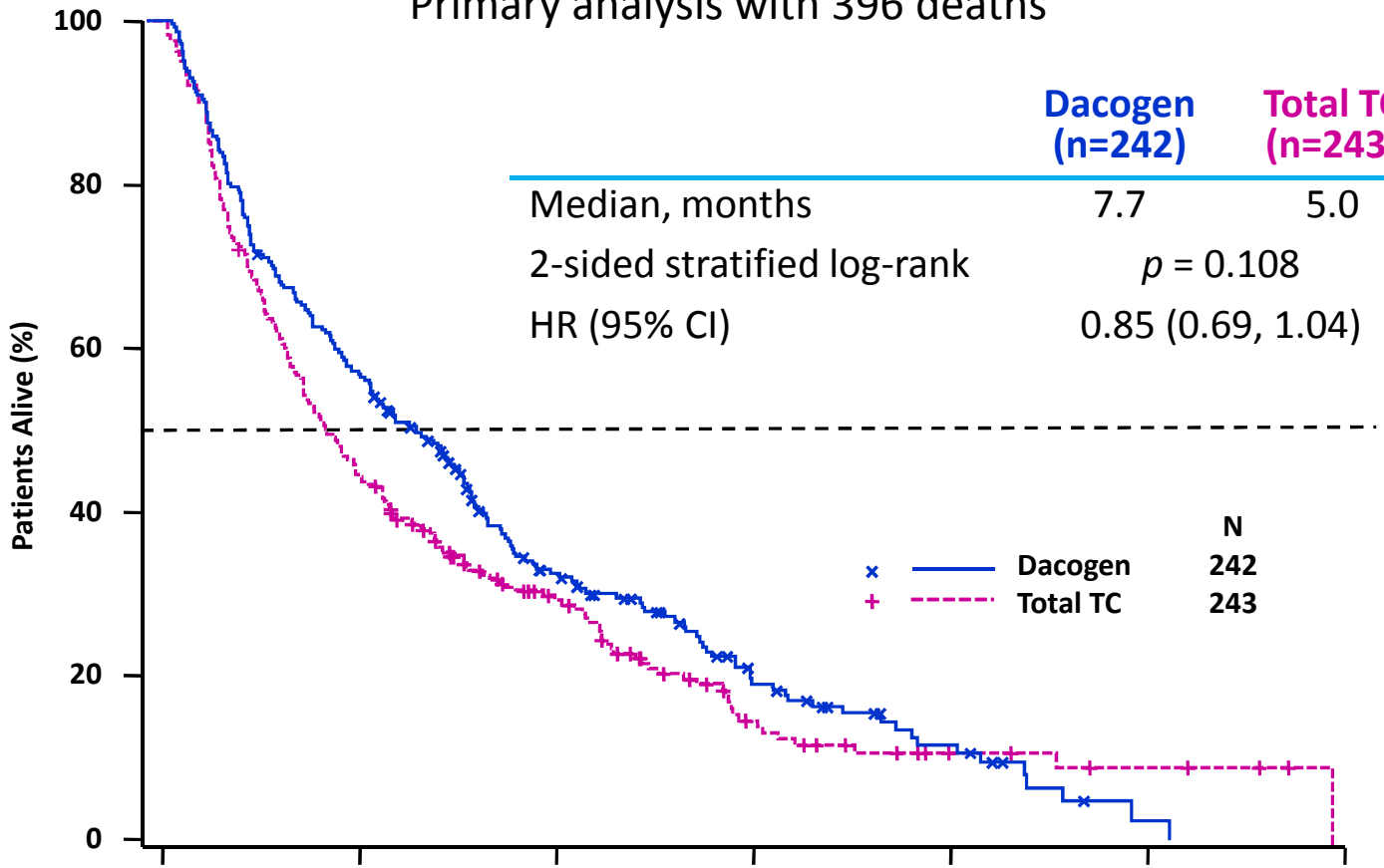
Tsub02, tsub20, tsub21 for each region

Primary Analysis of Overall Survival

Study 016 (Primary Analysis, 2009)

Primary analysis with 396 deaths

	Dacogen (n=242)	Total TC (n=243)	Delta
Median, months	7.7	5.0	2.7
2-sided stratified log-rank	$p = 0.108$		
HR (95% CI)	0.85 (0.69, 1.04)		



No. of Patients at Risk							
Dacogen	242	137	65	28	12	1	0
Total TC	243	107	55	19	7	4	0

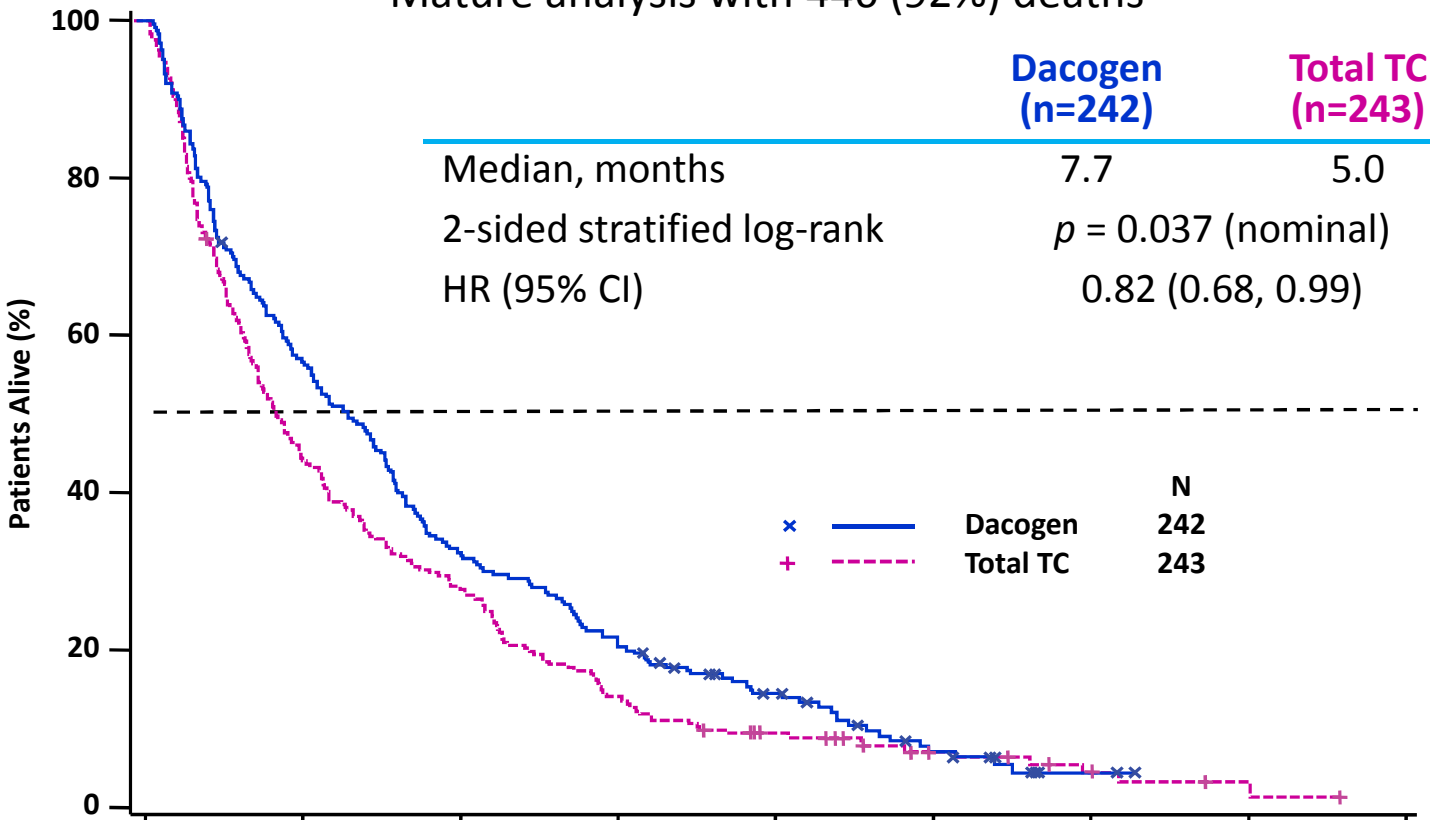
SCE Fig 1; Module 5.3.5.1.1\DACO-016 CSR\Table 23

Updated Overall Survival

Study 016 (Updated Analysis, 2010)

Mature analysis with 446 (92%) deaths

	Dacogen (n=242)	Total TC (n=243)
Median, months	7.7	5.0
2-sided stratified log-rank	p = 0.037 (nominal)	
HR (95% CI)	0.82 (0.68, 0.99)	



No. of Patients at Risk									
Dacogen	242	137	78	50	28	11	2	0	0
Total TC	243	107	68	35	20	10	4	2	0

SCE Fig 2; Module 5.3.5.1.1\DACO-016 CSR\Figure 6

Subsequent Disease-Modifying Therapy (DMT)

Study 016 (Primary Analysis, 2009)

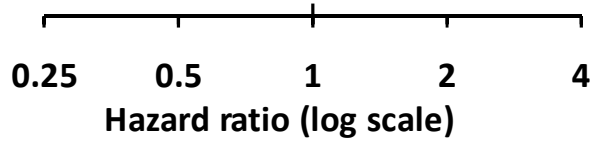
Subsequent therapy	Patients, n (%)	
	Dacogen (n=242)	Total TC (n=243)
Induction chemotherapy	25 (10.3)	25 (10.3)
Hypomethylating agents	6 (2.5)	19 (7.8)
5-azacitidine	4 (1.7)	14 (5.8)
Dacogen	2 (0.8)	5 (2.1)

- Median time to DMT shorter in TC (4 months) than Dacogen (6 months) arm
- Sensitivity analyses show DMT use affects primary analysis
  - OS nominally significant if censored at time of DMT use

Study 016 CSR, Table 21. Updated 10/5.

Overall Survival, Subgroup Analysis (1)
Study 016 (Primary Analysis, 2009)

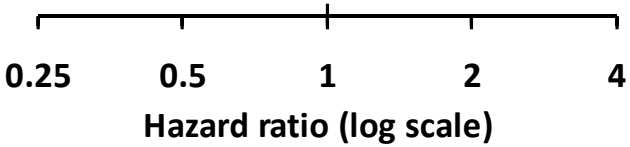
Subgroup	N	HR	*p* value	Median Dacogen	Median Total TC
All Patients	485	0.85	0.108	7.7	5.0
Type of AML					
De novo AML	312	0.73	0.018	8.0	5.2
Secondary AML	171	0.91	0.605	7.1	4.9
Baseline bone marrow blasts (%)					
≥ 20 to ≤ 30	123	1.09	0.711	8.0	6.1
> 30	347	0.74	0.013	7.1	4.3
Baseline cytogenetic risk					
Intermediate risk	306	0.79	0.071	9.4	6.0
Unfavorable risk	174	0.92	0.590	5.7	3.1



Study 016 CSR Fig 13

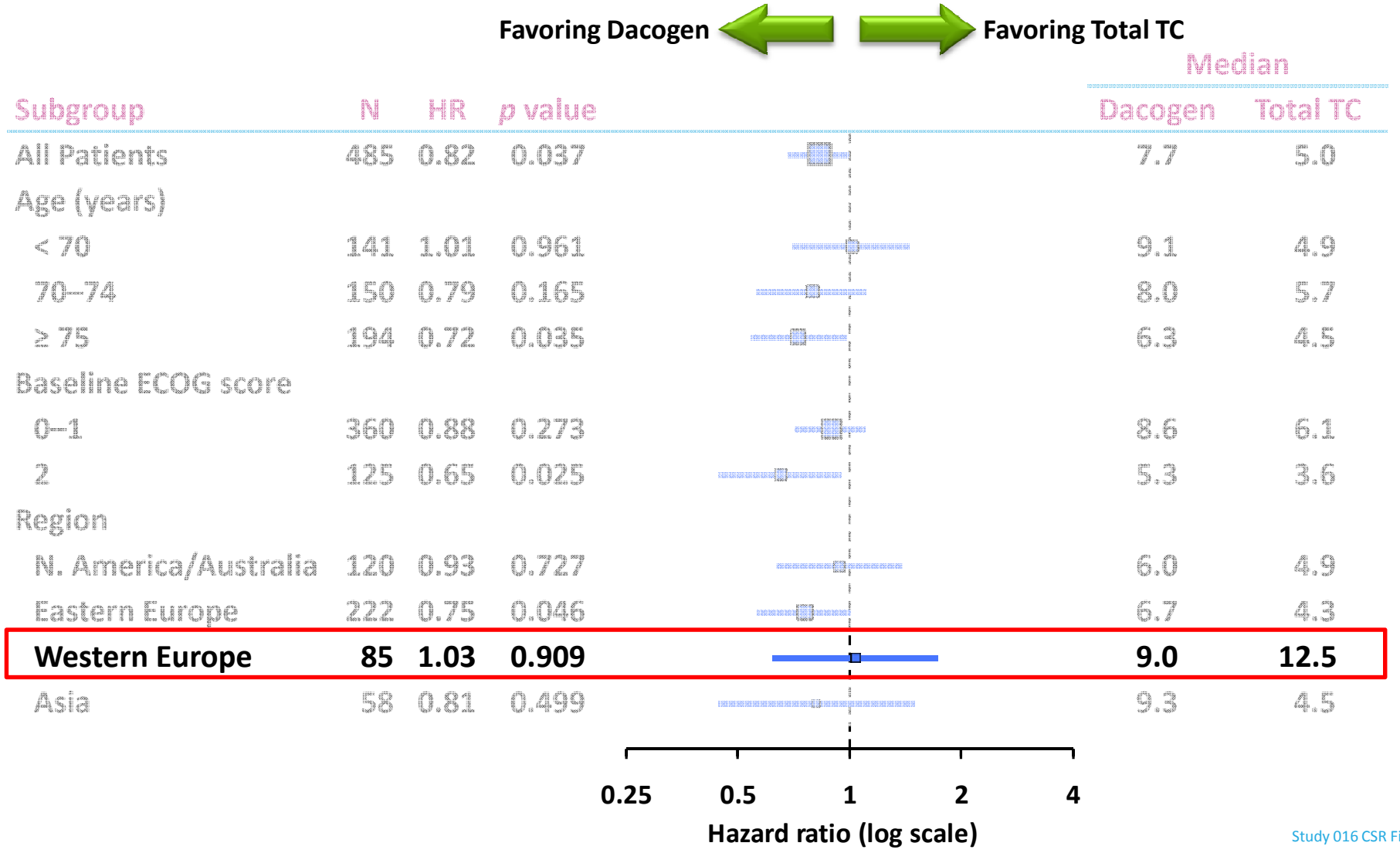
Overall Survival, Subgroup Analysis (2)
Study 016 (Primary Analysis, 2009)

Subgroup	N	HR	*p* value	Median Dacogen	Median Total TC
All Patients	485	0.85	0.108	7.7	5.0
Age (years)					
< 70	141	0.99	0.950	8.7	4.9
70–74	150	0.79	0.221	8.0	5.7
≥ 75	194	0.78	0.125	6.3	4.5
Baseline ECOG score					
0–1	360	0.90	0.387	8.7	6.1
2	125	0.71	0.093	5.3	3.6
Region					
N. America/Australia	120	0.91	0.631	6.0	4.9
Eastern Europe	222	0.73	0.048	6.7	4.3
Western Europe	85	1.43	0.239	9.1	14.4
Asia	58	0.83	0.552	9.3	4.5



Study 016 CSR Fig 13

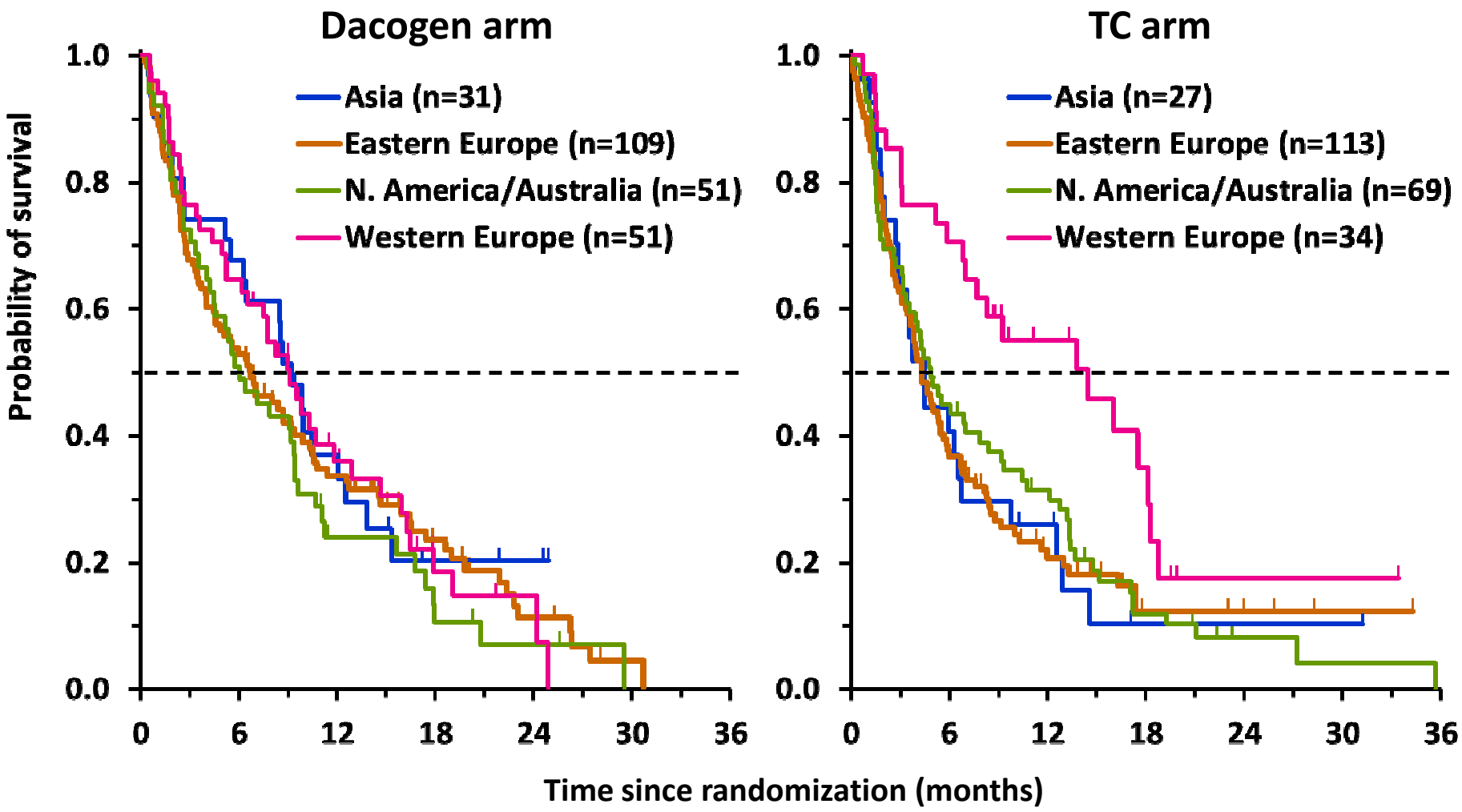
Overall Survival, Subgroup Analysis
Study 016 (Clinical Cutoff, 2010)



Study 016 CSR Fig 13

Overall Survival by Region—ITT Analysis

Study 016 (Clinical Cutoff 2009)



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Best Overall Response by Expert Review and Durability of Response

Study 016

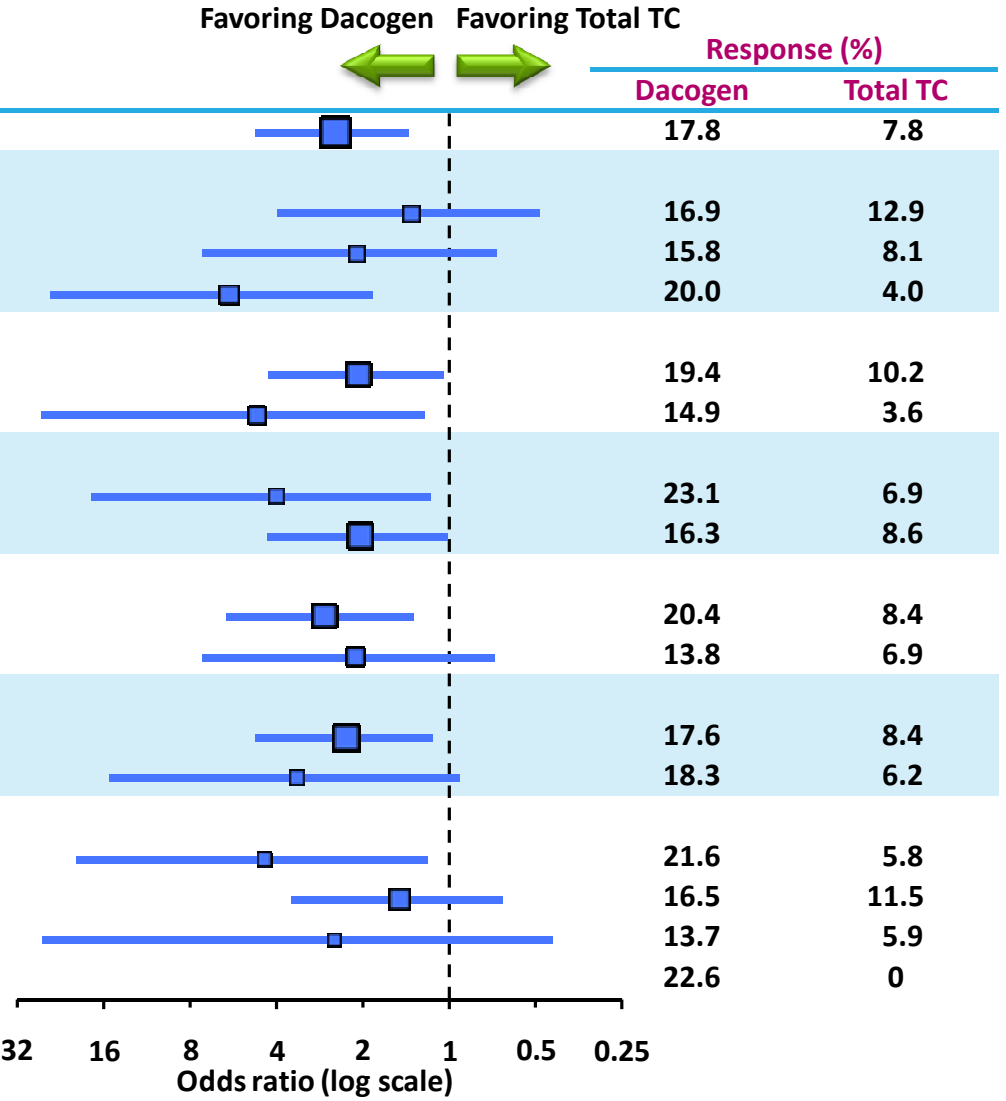
Best response	Patients, n (%) Dacogen (n=242)	Total TC (n=243)	Odds ratio (95% CI)	*p* value
CR	38 (15.7)	18 (7.4)	2.3 (1.25, 4.47)	0.004
Median RFS,[a] months (95% CI)	8.3 (4.6, 11.4)	6.7 (2.9, 13.4)		
CRp	5 (2.1)	1 (0.4)		
CR + CRp	43 (17.8)	19 (7.8)	2.5 (1.40, 4.78)	0.001
Median duration of response (CR + CRp), months (95% CI)	8.3 (6.2, 11.4)	12.9 (4.2, NE)		

CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with incomplete platelet recovery; CI = confidence interval.

a: Based on patients achieving a CR

Response (CR+CRp) Subgroup Analysis

Study 016



Subgroup	N	OR	*p* value	Response (%) Dacogen	Response (%) Total TC
All patients	485	2.55	0.001	17.8	7.8
Age (years)					
< 70	141	1.38	0.637	16.9	12.9
70–74	150	2.13	0.209	15.8	8.1
≥ 75	194	5.94	0.001	20.0	4.0
Type of AML					
De novo AML	312	2.12	0.026	19.4	10.2
Secondary AML	171	4.74	0.016	14.9	3.6
Baseline bone marrow blasts (%)					
≥ 20 to ≤ 30	123	4.05	0.023	23.1	6.9
> 30	347	2.07	0.034	16.3	8.6
Baseline cytogenetic risk					
Intermediate risk	306	2.78	0.003	20.4	8.4
Poor risk	174	2.16	0.212	13.8	6.9
Baseline ECOG score					
0-1	360	2.32	0.012	17.6	8.4
2	125	3.42	0.053	18.3	6.2
Region					
North America/Australia	120	4.47	0.013	21.6	5.8
Eastern Europe	222	1.52	0.335	16.5	11.5
Western Europe	85	2.55	0.305	13.7	5.9
Asia	58	NE	0.012	22.6	0

Progression-Free and Event-Free Survival

Study 016 (Primary Analysis, 2009) ITT Population

Analysis	Dacogen (n=242)	Total TC (n=243)
Median PFS, months (95% CI)	3.7 (2.7, 4.6)	2.1 (1.9, 3.1)
	HR = 0.75 (0.62, 0.91) nominal P^a = 0.003	
Median EFS, months (95% CI)	3.5 (2.5, 4.1)	2.1 (1.9, 2.8)
	HR = 0.75 (0.62, 0.90) nominal P^a = 0.003	

Disease progression was based on bone marrow and/or peripheral blast counts, or evidence of new extramedullary disease.

Protocol-defined events for determination of event-free survival (EFS) were treatment failure (discontinued treatment due to death, disease progression, or adverse event), relapse from a morphologic CR, death from any cause, or lost to follow-up.

a: Stratified log-rank

Patient Management by Region

Study 016 (Primary Analysis, 2009)

	E Europe (n=222)	N Am/Australia (n=120)	W Europe (n=85)	Asia (n=58)
Transfusions per patient-month (ITT)				
RBCs	1.79	1.70	1.48	2.59
Platelets	1.37	1.26	1.38	3.21
Systemic anti-infective therapy, n (%) (treated patients)	n=221 204 (92)	n=114 98 (86)	n=83 70 (84)	n=57 52 (91)
Subsequent DMT, % pts (ITT)				
Induction chemotherapy	11	6	9	19
Hypomethylating agents	0	8	19	0

TransfusPtMn_itt.doc;; AntiInfectCM_safety.doc

Response to FDA Sensitivity Analysis of Regional Effect

- FDA presented a sensitivity analysis of OS adjusting only for region
  - Conventional sensitivity analyses would adjust for important clinical parameters (e.g., age, cytogenetic risk, ECOG, AML type)
  - When these parameters are accounted for in sensitivity analyses along with region, the results are consistent with the primary analysis
- Western Europe in 2009 primary analysis appears to be an outlier
  - Median OS of 14 months in TC arm inconsistent with other regions
  - Hazard ratio changed from 1.43 in 2009 to 1.03 in 2010
- Response rate consistently favors Dacogen across regions

Study Design
Study 017

Patients (n=55)

- Age ≥ 60 years
- Newly diagnosed de novo or secondary AML
- ECOG performance status of 0-2
- Intermediate- or unfavorable-risk cytogenetics

→

Dacogen
20 mg/m^2 by 1-hour IV infusion once daily for 5 consecutive days every 4 weeks

Primary endpoint = morphologic CR rate (ITT) by expert assessment based on IWG criteria (Cheson BD, et al. 2003)

Response
Study 017

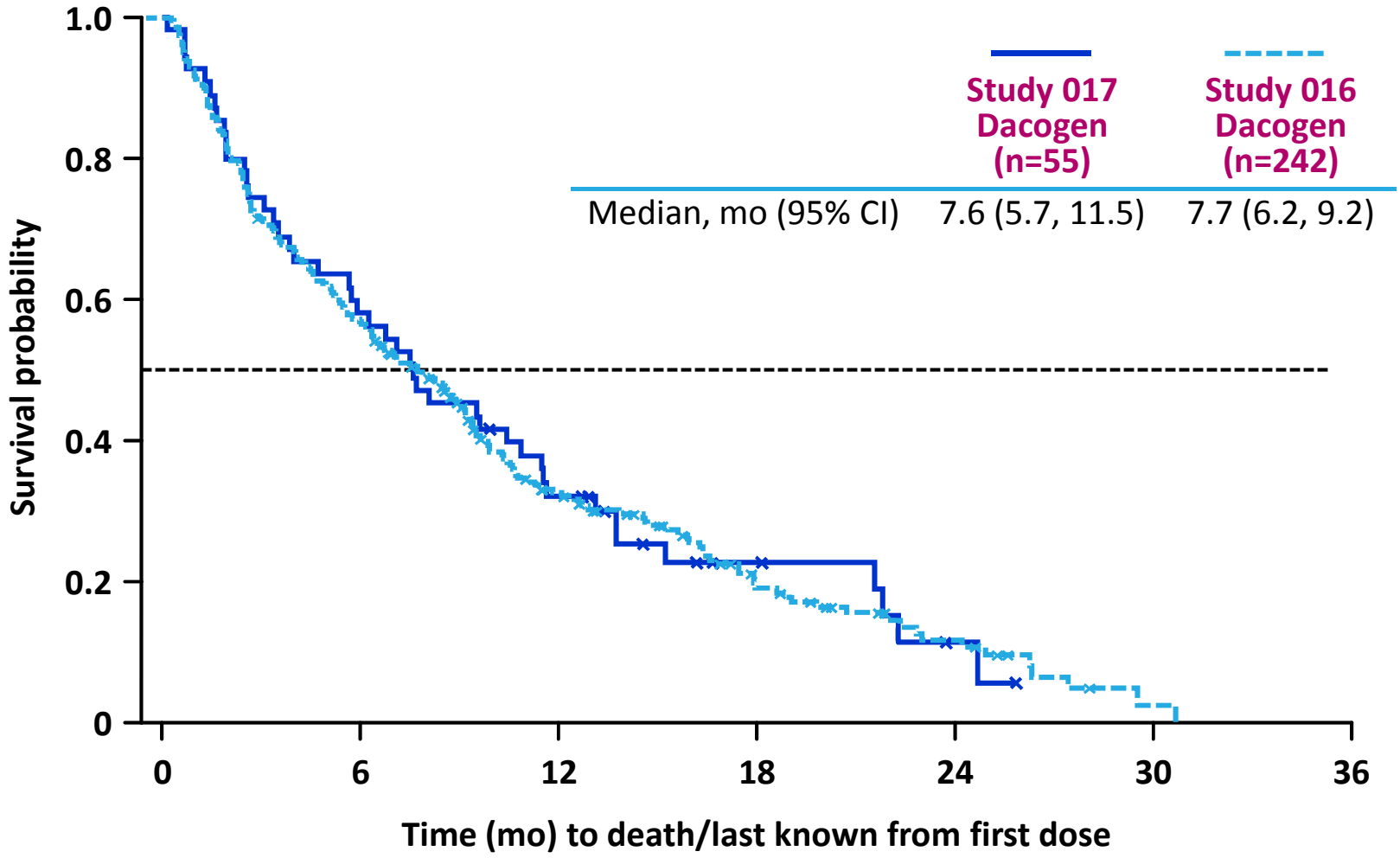
Best Response	Patients, n (%) (N=55)	95% CI	Study 016 Dacogen (n=242)
Morphologic CR	13 (23.6)	(13.2, 37.0)	38 (15.7)
Cytogenetic CR	5/34 (14.7)	(5.0, 31.1)	
CRi	1 (1.8)	(0.0, 9.7)	24 (9.9)

CR = complete remission; CRi = complete remission with incomplete blood count recovery.

SCE Table 6, 14; 017 CSR Module 2.7.3 Table 7.

Overall Survival

Studies 017 and 016 (ITT Population)



Efficacy Conclusions (1)

- Pre-specified primary OS analysis (396 events)
  - 2.7-month improvement in median OS (7.7 vs 5.0 months) HR = 0.85 (p = 0.108)
- Updated OS analysis (446 events, 92%)
  - 2.7-month improvement in median OS (HR = 0.82; nominal p = 0.037)
  - Supports that OS benefit is real treatment effect
- Consistent OS benefit across most subgroups
  - Regional findings likely represent variability in small, nonrandomized subgroups

Efficacy Conclusions (2)

- Dacogen significantly improved CR + CRp rate vs TC with durable responses
  - Median RFS = 8.3 months in Dacogen arm
- Dacogen significantly improved EFS and PFS ($p = 0.003$) versus TC
- Median OS and CR rates in Study 016 supported by results of Study 017
- Totality of the efficacy data provide evidence of a clinically meaningful treatment effect in elderly patients with AML

Safety

(XXXXX) Source

Extent of Exposure to Study Medication

Study 016 (Safety Population)

	Dacogen (n=238)	Cytarabine (n=208)
Number of cycles, n		
Median	4.0	2.0
Range	1.0–29.0	1.0–30.0
Treatment duration, months		
Median	4.4	2.4
Range	0–30	0–28
Total exposure, pt-months	1816.9	1053.5

- The duration of observation for safety was approximately two-fold longer in the Dacogen arm than in the TC arm
- Safety data are presented without adjustment for differences in exposure

Study 016 CSR Table 35; ISS Table 2.1.1

Most Common Treatment-Emergent AEs (All Grades) Occurring in ≥ 20% of Patients

Study 016 (Safety Population)

	Patients, %			
Preferred term	Dacogen (n=238)	Total TC (n=237)	Cytarabine (n=208)	SC (n=29)
Pyrexia	49	37	39	21
Thrombocytopenia	45	37	40	14
Anemia	41	31	34	14
Febrile neutropenia	35	23	26	0
Neutropenia	33	21	23	3
Diarrhea	29	23	24	17
Nausea	28	29	31	17
Hypokalemia	27	19	19	17
Pneumonia	25	22	22	17
Constipation	24	16	17	7
Disease progression	23	25	27	10
Leukopenia	22	11	13	0
Cough	22	17	18	10
Peripheral edema	22	18	20	7

SCS Table 10; ISS Table 4.2.

Most Common Grade 3/4 TEAEs (> 5% Patients)

Study 016 (Safety Population)

	Patients, %			
Preferred Term	Dacogen (n=238)	Total TC (n=237)	Cytarabine (n=208)	SC (n=29)
Thrombocytopenia	40	33	35	14
Anemia	34	25	27	14
Febrile neutropenia	32	22	25	0
Neutropenia	32	18	20	3
Pneumonia	21	18	19	14
Leukopenia	20	8	10	0
General physical health deterioration	13	16	16	17
Hypokalemia	11	10	9	17
Pyrexia	10	8	8	10
Dyspnea	7	6	5	10
Urinary tract infection	6	3	2	3
Sepsis	6	4	4	3
Septic shock	6	2	2	0

ISS Tables 4.3.2 and 4.3.3

Common Grade ≥ 3 TEAEs in First 2 Cycles

Study 016 (Safety Population)

	Pts on Treatment, n	Patients, %			
		Febrile neutropenia	Infection	Pneumonia	Thrombo-cytopenia
Cycle 1					
Dacogen	238	13	29	8	25
Cytarabine	208	15	32	8	26
Supportive care	29	0	10	7	3
Cycle 2					
Dacogen	186	12	25	7	19
Cytarabine	151	10	22	6	23
Supportive care	17	0	6	0	6

Worst CTCAE Grade 3 or 4 Hematologic Toxicity at Baseline and During Study Treatment

Study 016 (Safety Population)

	Patients, %							
	Dacogen (n=238)		Total TC (n=237)		Cytarabine (n=208)		SC (n=29)	
	Baseline	On-study	Baseline	On-study	Baseline	On-study	Baseline	On-study
Anemia	16	54	13	43	12	43	17	45
Neutropenia	58	82	58	68	60	72	48	45
Thrombocytopenia	42	82	44	80	42	81	55	69
WBC	29	71	30	52	32	54	21	31

CTCAE = Common Terminology Criteria for Adverse Events; SC = supportive care, TC = patient's choice of treatment with physician's advice; WBC = white blood cell count.

AEs Leading to Discontinuation and Early Deaths (30-Day All-Cause Mortality)

Study 016 (Safety Population)

	Patients, n (%)			
	Dacogen (n=238)	Total TC (n=237)	Cytarabine (n=208)	SC (n=29)
Total AEs leading to discontinuation	98 (41.2)	100 (42.2)	97 (46.6)	3 (10.3)
Death within 30 days after first treatment	21 (9)	19 (8)	17 (8)	2 (7)
Disease progression	4 (2)	5 (2)	5 (2)	0
Adverse experience	17 (7)	14 (6)	12 (6)	2 (7)

SCS Table 22; Module 2.7.4 Table 22.

Safety Conclusions

- Dacogen was well tolerated
  - The safety profile was consistent with the known safety profile in patients with MDS
  - There were no new safety signals
- As expected, the most prevalent AEs were related to myelosuppression (cytopenias and febrile neutropenia)
- Adverse events were generally manageable with routine medical care
- Discontinuations due to an AE were similar in both treatment arms
- The incidence of 30-day all-cause mortality was low (9%) and similar in both treatment arms

DACOGEN® (decitabine) Benefit/Risk

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Unmet Clinical Need for Older AML Patients

- No improvement in therapy for patients ≥ 65 years of age with AML in decades; no new approvals in US since 2000 (Mylotarg)
- Population in Study 016 characterized by
  - Relatively advanced age (median, 73 years)
  - Intermediate- or unfavorable-risk cytogenetics
  - Moderate PS (64% ECOG PS 1 or 2)
  - Low WBC (median, 3.4 giga/L)
- Current management of this patient population
  - Poor outcomes from induction chemotherapy
  - Often does not receive induction chemotherapy (or any therapy)
- There is a need for a low-intensity treatment option

Totality of Data Support Dacogen Efficacy

	Endpoint	Result (Dacogen vs TC)
Primary	Overall Survival (396 events)	Median 7.7 vs 5.0 months (HR = 0.85; *p* = 0.108)
	Updated OS (446 events, 92%)	Median 7.7 vs 5.0 months (HR = 0.82; nominal *p* = 0.037)
Secondary	CR + CRp	17.8% vs 7.8% OR = 2.5 (*p* = 0.001)
Tertiary	RFS PFS EFS	Median 8.3 months Median 3.7 vs 2.1 months (HR = 0.75; *p* = 0.003) Median 3.5 vs 2.1 months (HR = 0.75; *p* = 0.003)
Supportive Study 017	CR rate Median OS	23.6% 7.6 months

Dacogen Demonstrated an Acceptable Safety Profile

- Toxicity was consistent with the known safety profile in patients with MDS, and comparable to that of low-dose cytarabine
- Numerical increase in myelosuppression events that are manageable in this disease setting
- Treatment duration was 2-fold longer with Dacogen than with TC
- Discontinuations due to an AE were similar in both treatment arms
- 30-day all-cause mortality was low compared with standard induction chemotherapy, and comparable to low-dose cytarabine

Dacogen Has a Favorable Benefit-Risk Profile in Elderly AML Patients

- Totality of data support Dacogen efficacy and safety in this setting
  - Clinically meaningful improvement in OS
  - Improves rate of CR + CRp and induces durable CRs
  - Efficacy consistently observed across multiple endpoints and most subgroups
  - Well tolerated
    - Safety profile consistent with known safety profile in MDS